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Habituation as parameter for prediction of mental development in healthy preterm infants: an electrophysiological pilot study

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Abstract

The aim of this prospective pilot study was to evaluate the predictive value of discrimination and habituation, which was measured by mismatch negativity in 17 healthy very preterm (mean gestational age: 27.4 weeks; range 25.0 – 31.3) and 16 term (mean gestational age 40.3 weeks; range 37.9 – 41.7) born infants at term equivalent age. Developmental outcome was measured by Bayley Scales of Infant Development-I in 13 preterm and 13 term born children at a mean age of 21.7 months (± 2.18) and 18.5 months (± 1.9) respectively. No differences in amplitude and latency of the mismatch negativity were found between both groups at term equivalent age. Within the preterm group habituation capacity was positively correlated with the Mental Developmental Index MDI ($r=0.654$; $p=0.008$) and Performance Developmental Index ($r=0.482$; $p=0.048$) at 21 months. Early learning capability, as measured by habituation, may be associated with a better prognosis for early mental development in healthy preterm infants.

Keywords: extreme prematurity, mental development, auditory event-related potentials, mismatch negativity, habituation

Abbreviations

AERP	Auditory Event Related Potential
BSID-I	Bayley Scales Infant Development I
MMN	Mismatch Negativity
dMMN	Difference in Mismatch Negativity between first vs. third stimulus block
GA	Gestational Age
NICU	Neonatal Intensive Care Unit

Introduction

Preterm birth is the main cause of infant mortality and a very important risk factor for the development of intellectual disability (1). Whereas individual prediction of cerebral palsy - the severe form of a movement disorder following prematurity - by clinical bed-side procedures is already possible with sufficient validity within the first 3 to 6 months of life (2,3), accurate identification of individual children with increased risk for cognitive impairments is still a challenge because of the difficulties in finding any valid bed-side tests of estimating cognitive abilities in infancy (4). Closing this diagnostic gap is therefore of utmost clinical importance in long-term follow-up of preterm children (5). Early identification of preterm infants at risk for neuropsychological sequelae is particularly relevant because early intervention programs are found to be effective up to preschool age (6). Even if the concept of brain plasticity recommends an early start of intervention, “high rate of attrition in routine clinical follow-up and consequent difficulty in accurately determining rates of delay highlight challenges for centers providing ongoing care” (7). Offering these programs to all very preterm children is not feasible in many countries due to limited resources. In addition in some countries, such as Switzerland, a routinely evaluation of the development of preterm infants is offered, but not an early intervention for all children. Thus, there is potential need to develop diagnostic tools which allow risk-stratification by early identification of preterm infants at increased risk for mental impairment, who might possibly benefit the most from such intervention programs.

Numerous studies show that several event-related components in an auditory oddball paradigm are easily measurable and indicative of mental functioning in neonates (8-10). Moreover sound discrimination tasks, used in the Neonatal Intensive Care Unit (NICU), appear to be predictive of cognitive outcome in preterm infants at two years of age (12). Such an auditory oddball paradigm consists of presenting sequences of repetitive “standard” tones,

sporadically interrupted by “deviant” tones, resulting in an auditory event-related (AERP) component called mismatch negativity (MMN). This ERP-component is calculated by subtracting the average ERP of the standard tones from the average ERP of the deviant tones. The by subtraction resulting difference waveform is known to have a negative amplitude peaking between 100 and 250 ms post deviant stimulus onset in adults (13). It is interpreted as a pre-attentive cognitive discrimination ability and can already be observed from 30 weeks of gestational age (GA) onwards (14).

Preterm infants may show a diminished capability for habituation and dishabituation as early signs of delay in mental processing such as encoding, attention, discrimination, and memory (15). Nevertheless until now habituation and its predictive value for later mental development of very preterm children has not yet been studied in an electrophysiological setting. Therefore we aimed to assess discrimination, as an early pre-attentive parameter, and habituation, as an early parameter of learning, measured by auditory ERPs in very preterm compared to healthy term born infants in a clinical routine setting. Testing the predictive value of habituation in preterm infants at term-equivalent age for the mental development we correlate the habituation capability at this age, measured by dMMN, with the developmental level at corrected age of 21 months.

Methods

Participants and procedure

In this prospective pilot-study preterm infants were recruited at the Neonatal Intensive Care Unit (NICU) of the University Children’s Hospital Basel and healthy term born infants were recruited at the child-bed ward of the Division of Gynaecology and Obstetrics of “Bruderholzspital” in the canton Basel-Landschaft. We examined 17 very preterm infants and 16 healthy term born infants at a mean gestational age of 40.8 weeks (range: 38.1-43.0).

Preterm infants with severe brain lesions (i.e. > grade II intracerebral hemorrhages, neonatal seizures), genetic syndromes, or confirmed congenital infection were excluded from the study to avoid a heterogeneous cohort. The cohort characteristics are documented in Table 1. Routinely in all infants and neonates transient-evoked otoacoustic emissions were recorded and analyzed, before discharge from the hospital (36-42 weeks of GA). All participants fulfill the “pass” criterion. Even if this procedure doesn’t allow to quantify the hearing level, it is accepted to be demonstrating a normal cochlear function (16).

Follow-up was conducted and 13 preterm and 13 term born children were tested with regard to developmental outcome at a corrected mean age of 21.7 months (± 2.18) and 18.5 months (± 1.9) respectively. Thus there was a drop-out of 4 preterm and 3 term born children due to moving of the families, including one family with preterm triplets.

The Ethics Committee of Basel approved the study protocol, parents gave written informed consent, and the study has been carried out in accordance with the Declaration of Helsinki.

Auditory event-related potentials

The AERPs were conducted with electrodes located according to the International 10-20 system at midline electrode sites (Fz, Pz, and Oz) and referenced to the left-sided mastoid electrode A1. To control for artifacts by eye movements, one electrode was located at the lower outer side of the left eye. The passive auditory oddball paradigm was used in the study to elicit AERPs. It consists of presenting two tones with different frequencies (Hz). The standard (i.e. frequently occurring) tone was 1000 Hz and the deviant (i.e. rarely occurring) tone 2000 Hz, both presented in a pseudo-randomized order. The standard tone occurred with a probability of 85%, while the deviant tone occurred with a probability of 15%. The stimulus frequency was 0.9 Hz and the intensity 80 dB normal hearing level (nHL). In the experimental setting, three blocks of 500 tones were presented via headphones to the silent awake or sleeping infants. A break of two minutes was taken between each block. The ERPs were

recorded with the Viking Select 4-channel in a bed-side setting. Even if the use of this simple equipment with only four active electrodes implicated some limitations, such as renouncement of information about laterality or automatically grand averaging, it was used since it is an equipment which is available in the clinical setting of nearly all Neonatal Intensive Care Units, underlining the aspect of the feasibility of this data collection in daily routine on the ward. The data were acquired offline with a band-pass filter of 0.5 – 40 Hz and a sampling rate of 20 kHz. .

Data analysis

The artifact rejection was performed manually per stimulation block. Samples with an amplitude difference between rare and frequent tones of $>0.5 \mu\text{V}$ at the electrode under the eye were excluded, as indication of a relevant influence by eye blinks. The electrophysiological response was then averaged over the standard and the deviant tones independently for each of the 3 stimulus blocks.

In order to compute the Mismatch negativity (MMN), at first we manually identified the peak of the event-related potential in the time window between 150 and 300 ms after stimulus presentation for every proband. Thereafter the differences of the amplitude between rare and frequent tones were calculated, defining the MMN. (Figure 1) The resulting MMN is investigated regarding amplitude (in μV), latency (in ms) and polarity (negative or positive) and corresponds to the discrimination ability of the subjects. The habituation capability is then calculated by the difference in amplitude of MMN between the first and third stimulus block (dMMN).

Developmental outcome

The developmental outcome was measured by the Bayley Scales of Infant Development I (BSID I) (17) and the Mental Developmental Index (MDI) and Performance Developmental

Index (PDI) were computed. The examiners were blinded with regard to the electrophysiological data.

Statistical analysis

Statistical computations were performed using SPSS version 22.0 (IBM) for Windows. Pearson's Chi-squared test, calculation of Pearson's correlation coefficient, or t-test for independent cohorts were used accordingly. The significance level was set at $p < 0.05$ (two-tailed).

In respect to the proof-of-concept initiation of the study and the small sample size, no Bonferroni corrections were applied.

Results

MMN

No significant group differences in latency or mean amplitude of the MMN were found at the midline electrodes between preterm and term born infants. However, significantly more preterm infants showed a lower arbitrary chosen MMN amplitude of $< 2\mu\text{V}$ ($\chi^2 = 4.29$; $p = 0.038$) at Fz compared to term infants. In addition no significant difference was found in the habituation effect calculated by the dMMN during the first and the third stimulus block, just as no difference was observed in the frequency of a habituation or dishabituation effect between the groups (Table 2).

Outcome

The developmental outcome measured by BSID-I showed significant differences between the preterm and control group. In particular, both groups differed significantly on the MDI (74 ± 18.28 in the preterm group vs. 95 ± 10.78 in the control group; $t(19.5) = 3.49$; $p = 0.002$) and the PDI (89 ± 13.01 in the preterm group vs. 109 ± 8.9 in the control group; $t(24) = 4.57$;

$p < 0.001$). No differences were found in the behavioral scales: Orientation ($t(23) = -.30$; $p = 0.766$), emotion ($t(23) = 2.02$; $p = 0.568$), or motor quality ($t(23) = 2.14$; $p = 0.43$).

Correlations

Within the group of preterm infants no significant correlation was found between GA and amplitude or latency of MMN at any of the three electrode positions. However GA significantly correlated with dMMN at electrode position Fz ($r = 0.551$; $p = 0.013$), Cz ($r = 0.531$; $p = 0.017$), and Pz ($r = 0.478$; $p = 0.031$) (Table 3; Figure 2).

With regard to the developmental outcome test, MDI was significantly correlated with dMMN at the electrode position Cz ($r = 0.654$, $p = 0.008$), but not at position Fz ($r = 0.313$; $p = 0.149$) or Pz ($r = 0.145$; $p = 0.319$). PDI was also significantly correlated with dMMN at position Cz ($r = 0.482$; $p = 0.048$), but no correlation was observed between PDI and dMMN at position Fz ($r = 0.157$; $p = 0.304$) and Pz ($r = -0.047$; $p = 0.439$) (Figure 3).

Discussion

The main finding of our study is the association between the habituation capability (dMMN) and the mental and performance outcome subtest at the age of 21 months within the group of preterm infants. This positive relation suggests that the lower the habituation effect, the lower the scores on the mental and performance scale. The relationship between ERP-components and the BSID highlights the power of auditory event related measures in prediction of cognitive abilities (8,9,18), although we have taken into account the low statistical power of our study including the fact that no Bonferroni correction considering the number of electrodes were done, which would decrease the statistical significance. Other studies have found similar relationships between AERPs and cognitive outcomes even at later ages (10,12). We examined habituation, a variable that has not been adequately assessed in previous studies using auditory event-related potentials in preterm born children. In an older behavioral study (19) fast movement habituation was found to be related to higher scores on

the MDI. Habituation is regarded as the most elementary form of learning and can be observed in neonates in behavioral studies (15) as well as in neuroimaging studies (18,22). Since the competence of learning is an important constituent of cognitive development, it is a potentially useful predictor of neurodevelopmental outcomes in infants at greatest risk for cognitive impairment (22).

Our pilot study points to the possible early predictive value of habituation measured by MMN for later individualized developmental outcomes in very preterm infants. Moreover, it implies that this procedure might be useful as a simply applicable risk stratification tool in a bed-side setting. The fact that the closest correlation between the developmental level at age of 21 months and the habituation effect was documented at the Cz lead, could evoke some suggestions about the cortical function involved in the tasks. In respect of the small head circumference of the infants as well as the insufficient spatial resolution of electroencephalography from scalp electrodes, we disclaim this speculation at this point.

In contrast to most studies with larger samples sizes (20), in our study we found no differences regarding amplitude or latency of MMN in a passive auditory oddball paradigm between very preterm born and term born infants at neonatal age. Even though no significant group differences were found in mean values, using an arbitrary cut off amplitude value of $< 2\mu\text{V}$ more control infants exceeded this MMN limit than preterm infants. Often it is reported that the lower the gestational age, the lower the ERP-amplitudes (20). Lower amplitudes might indicate lower capacities in detection of sound differences, meaning a less pre-attentive discrimination ability, and therefore immaturity of the auditory system (21). Consequently our results suggest that only a subgroup of very preterm infants show reduced mental processing during discrimination tasks. In this way, measuring habituation as a possible predictor of cognitive impairment in early infancy might open the window for more targeted follow up neurodevelopmental therapies in certain newborns.

Contrary to what might have been expected the habituation capacity - defined by the reduction of the MMN amplitude between the first and third session (dMMN) - did not differ among the preterm as compared to the control children, neither between the first and second stimulus block, nor between the first and third stimulus block. As a limitation of our technical methods, we could not analyze a possible habituation effect within one single (i.e. the first) stimulus block. It is possible that habituation is a fast learning process, which could be detected only in a short time window. In addition, the failure to replicate this result might be due to limited statistical power in the present study and the fact that only a subgroup of preterm infants at higher risk might show this deficiency.

As expected, very preterm children showed lower scores in mental development compared to children born at term which is in line with existing evidence (23, 24).

Furthermore, dMMN was also related to the GA, meaning the earlier the infant is born, the lower the habituation effect and vice versa. Gestational age is an important risk factor in general and known to correlate with cognitive outcomes (12). Therefore in a larger sample size dMMN has to be confirmed as independent predictive variable. In addition infants with prematurity under 25 gestational weeks and higher risk of neurodevelopmental problems should be included for further testing the discussed hypothesis.

Beside the small sample size, the main constraint of this pilot study is that only three electrode positions were used and therefore does not provide us with many strong correlations between the ERP-components and the mental outcome test. Moreover the low number of participants and the drop-out for the outcome measurement at the age of 21 months leaves us with less data to support our prediction hypothesis. The outcome was only investigated in early childhood, so data from the subjects at a later age in their development would be interesting.

In conclusion, this proof-of-concept pilot study suggests the AERP-approach as a potentially valuable tool to assess early cognitive abilities, such as habituation, in neonates in a bed-side setting.

Declaration of interest

The authors declare that there is no conflict of interest

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Figure legends

Figure 1: Example of an averaged AERP of the first stimulus block of one participant. The maximum amplitude peaks between 150-300 ms are indicated at the midline electrodes (Fz, Cz, Pz) for rare (R, $n=75$) tones and the correspondent amplitude value for frequent (F, $n=425$) tones. By subtracting these amplitude values respectively, the MMN component is calculated

Figure 2 A-C:

Simple linear regression of the amplitude difference between MMN in the first stimulus block minus MMN in the third stimulus block (=habituation effect, dMMN) and gestational age at electrode position Fz (A), Cz (B), and Pz (C).

Figure 3 A-B:

Simple linear regression of the amplitude difference between MMN in the first stimulus block minus MMN in the third stimulus block (=habituation effect) and MDI (A) and PDI (B) at the electrode position Cz.

Table 1

Cohort characteristics: group differences tested by unpaired t-test and Chi-quadrat test.

	Preterm infants (N=17)	Term born infants (N=16)	p-values
GA at birth	27.4 weeks	40.3 weeks	<0.001*
mean (range)	(25.0 – 31.3)	(37.9 – 41.7)	
GA at examination	40.8 weeks	40.8 weeks	0.943
mean (range)	(38.4 – 43.0)	(38.1 – 42.0)	
Sex (m : f)	9 : 8	10 : 6	0.257
Birth weight	893g	3603g	<0.001*
mean (range)	(470 – 1530)	(2880 – 4300)	

* $p < 0.05$

Table 2

Latency, amplitude, frequency of low MMN amplitudes ($< 2 \mu V$), difference of the amplitude (habituation effect) of MMN between the first and second (dMMN 1-2) and between the first and the third stimulus block (dMMN 1-3), and frequency of dishabituation in both groups at the three electrode positions Fz, Cz, and Pz after unpaired t-tests.

		Preterm infants (N=17)	Term born infants (N=16)	p-values
Fz	MMN latency (ms) (mean \pm SD)	220.9 (\pm 42.8)	234.9 (\pm 27.3)	0.275
	MMN amplitude (μV) (mean \pm SD)	3.27 (1.88)	4.08 (\pm 1.71)	0.205
	Frequency MMN amplitude $< 2\mu V$ dMMN 1-2	4/17	0/16	0.038*
	amplitude (μV) (mean \pm SD)	-0.01 (\pm 1.53)	0.75 (\pm 1.93)	0.236
	Frequency of dishabituation dMMN 1-3	8/17	6/16	0.740
	amplitude (μV) (mean \pm SD)	0.42 (\pm 3.36)	1.33 (\pm 1.56)	0.330
	Frequency of dishabituation	7/17	3/16	0.127
	MMN latency ms (mean \pm SD)	204.3 (\pm 21.7)	213.3 (\pm 20.5)	0.230
	MMN amplitude (μV) (mean \pm SD)	4.22 (\pm 2.79)	4.65 (\pm 2.35)	0.644
Cz	Frequency MMN amplitude $< 2\mu V$ dMMN 1-2	4/17	1/16	0.144
	amplitude (μV) (mean \pm SD)	0.43 (\pm 2.50)	1.17 (\pm 2.38)	0.406
	Frequency of dishabituation dMMN 1-3	7/17	5/16	0.849
	amplitude (μV) (mean \pm SD)	0.63 (\pm 3.32)	0.65 (\pm 2.77)	0.986
	Frequency of dishabituation	9/17	6/16	0.288
	MMN latency ms (mean \pm SD)	213.9 (\pm 36.9)	205.0 (\pm 27.2)	0.438
	MMN amplitude (μV) (mean \pm SD)	2.90 (\pm 1.41)	3.08 (\pm 1.70)	0.743
	Frequency MMN amplitude $< 2\mu V$ dMMN 1-2	5/17	4/16	0.694
	amplitude (μV) (mean \pm SD)	0.20 (\pm 1.44)	1.0 (\pm 1.78)	0.179
Pz	Frequency of dishabituation	9/17	7/16	0.777
	dMMN amplitude (μV) (mean \pm SD)	0.23 (\pm 1.68)	0.30 (\pm 2.02)	0.915
	Frequency of dishabituation	7/17	8/16	0.723

* $p < 0.05$

Table 3

Pearson correlations between gestational age at birth (GA), mental developmental index (MDI), and performance developmental index (PDI) and the difference between MMN during the first and the third stimulus block (dMMN = habituation effect).

	GA	MDI	PDI
dMMN (μ V) at Fz	0.551*	0.313	0.157
dMMN (μ V) at Cz	0.531*	0.654*	0.482*
dMMN (μ V) at Pz	0.478*	0.154	0.047

* $p < 0.05$











